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The sensitivity of togaviruses to the effects of interferon (IF) appears to permit successful exploitation of IF inducers, whereas the relative insensitivity of arenaviruses to IF in vitro appears to correlate with the complete lack of success of lysine-stabilized poly(I)·poly(C) [poly(ICLC)] therapy in the monkey model. Noteworthy is the successful use of poly(ICLC) against fatal encephalitis caused by Japanese encephalitis virus in monkeys. Additional studies appear to be warranted to characterize further the role of IF and/or IF inducers in other model infections prior to studies in man.

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EFFECT OF INTERFERON ON TOGAVIRUS AND ARENAVIRUS INFECTIONS OF ANIMALS[1,2]

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INTRODUCTION

Viruses differ markedly with respect to their in vitro sensitivity to the effects of interferon (IF). In addition, there appears to be little correlation between in vitro IF sensitivity and virulence in vivo. Although there are some exceptions, the virulent togaviruses and arenaviruses are no more resistant to IF in vitro than avirulent, group-related viruses. There are data which might suggest a greater IF sensitivity of the attenuated Venezuelan equine encephalitis (VE) vaccine strain than the parent virus (7, 8), but in general it is not possible to correlate togavirus IF sensitivity to virulence. Togaviruses are considered generally to be very sensitive to the effects of IF (3, 15).

There is a paucity of information regarding the IF sensitivity of arenaviruses. It appears, however, that the IF sensitivity of arenaviruses is not apparently related to virulence. Previous reports have shown that lymphocytic choriomeningitis (LCM) virus, a member of the arenavirus group, does not induce IF in mice, and have described the role of IF in the development of the well-characterized carrier state of infection (6, 16). Recently Luscri characterized several arenaviruses with respect to their sensitivity to human IF when assayed in African green monkey kidney (BS-C-1) cell cultures (16). Arenaviruses were less sensitive than vesicular stomatitis (VS) virus, with Tacaribe, Machupo, and LCM viruses being 10-, 100-, and >100-fold less sensitive, respectively, than VS virus (16). When assayed in LLC-MK_2 cell cultures, Tacaribe virus was only twofold less sensitive than VS and VE viruses, and equally as sensitive as yellow fever (YF) virus (16).

The relative IF sensitivity of viruses may have an important bearing on the efficacy of IF inducers in the treatment of virus-induced disease. The greater sensitivity of togaviruses to IF roughly correlates with their in vivo sensitivity to IF inducers. VE and YF virus infections of mice were successfully treated by the prophylactic administration of tilorone hydrochloride or poly(I)·poly(C) stabilized with carboxymethyl-

keys given poly(ICLC) initially on day 0 were detectably viremic on day 5. These monkeys had significantly greater viremia than that of untreated control monkeys on days 10 ($P < 0.05$ one-way analysis of variance) and 12 ($P < 0.01$). The mean time to death was similar to that for virus control monkeys. When treatment was initiated on day 1, viremia was again significantly greater than that of control monkeys on days 10 ($P < 0.05$) and 12 ($P < 0.01$). With initial treatment on day 7, the mean time to death was day 15, and one of three monkeys survived. Since occasional infected, untreated monkeys survive, it is not possible to attribute this survival to poly(ICLC) treatment. The viremia response at these monkeys given late treatment was not significantly different from that of untreated, control monkeys.

Untreated virus control monkeys had detectable interferon as early as day 3, and all three monkeys had detectable IF by day 5 (50 to 125 units) 2 days earlier than viremia was detected (Table 1). In addition, peak IF (up to 700 units) occurred prior to peak viremia. Two of three monkeys treated initially on day 0 did not have detectable interferon until day 5, coincident with onset of viremia. IF response in the monkeys initially treated on day 1 was similar to monkeys treated on day 0. When treatment was delayed until day 7, the IF response paralleled that of the untreated monkeys. The appearance of IF in the serum of untreated monkeys prior to the onset of viremia was unexpected and is probably a further indication that the pathogenesis of the more IF-resistant arenavirus infections cannot be favorably altered by treatment with poly(ICLC). Poly(ICLC) treatment of Machupo virus infection of monkeys appears to be clearly contraindicated, since monkeys treated early in infection have significantly higher viremias than untreated, virus control monkeys. A possible explanation for the higher viremias is that IF and/or poly(ICLC) either altered or stimulated the production of certain cell types that are target tissues for replication of Machupo virus.

SUMMARY

The sensitivity of togaviruses to the effects of IF appears to permit successful exploitation of IF inducers, whereas the relative insensitivity of arenaviruses to IF in vitro appears to correlate with the complete lack of success of poly(ICLC) therapy in the monkey model. Noteworthy is the successful use of poly(ICLC) against fatal encephalitis caused by JE virus in monkeys. Additional studies appear to be warranted to characterize further the role of IF and/or IF inducers in other model infections prior to studies in man.

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Footnotes

[1] In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on the Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Research Council. The facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

[2] The views of the author do not purport to reflect the positions of the Department of the Army or the Department of Defense.

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Table 1. Effect of poly(ICLC) treatment on the viremia and interferon responses of rhesus monkeys infected with Machupo virus

Group (Days of treatment)	Monkey	Viremia (PFU/ml) [Interferon (Units/ml)] $\log_{10}$									Mean peak day		Day of Death
		0	3	5	7	10	12	14	17	21	Viremia	Interferon	
I (None)	A	–	–	–	2.88	3.60	2.40	3.60	3.11	1.00			21
		–	–	[2.1]	[2.8]	[2.4]	[1.4]	[2.1]	[2.1]	[0.7]			
	B	–	–	–	2.48	3.18	3.18	3.25	4.11	2.76	12		21
		–	[1.9]	[1.7]	[2.8]	[2.4]	–	–	–	–		7	
	C	–	–	–	2.00	3.23	3.30	3.95	4.15	D			18
		–	–	[2.1]	[2.8]	[2.8]	[2.4]	[1.4]	[1.4]				
II (0–5, 7, 10, 12)	D	–	–	–	–	3.54	4.23	5.18	6.00	D			19
		[2.3]	[2.1]	[0.7]	[0.9]	–	[3.5]	[2.8]	[2.1]				
	E	–	–	3.18	4.23	5.58	5.36	4.93	D		17		16
		–	–	[2.1]	[3.1]	[2.8]	[2.1]	[1.6]				12	
	F	–	–	2.45	3.90	5.20	5.08	4.52	3.34	2.51			27
		–	–	–	[2.8]	[2.8]	[1.4]	–	–	–			
III (1–5, 8, 10, 12)	G	–	–	–	4.67	4.70	5.04	3.93	4.68	D			20
		–	[1.4]	[2.8]	[2.8]	[2.8]	[2.1]	–	–				
	H	–	–	–	3.18	5.28	4.85	6.00	5.62	D	7		18
		–	–	(1.4)	[3.5]	[2.8]	[1.6]	[1.6]	[1.6]			7	
	I	–	–	–	4.15	4.48	5.28	4.15	5.23	D			19
		–	[2.1]	[2.8]	[3.7]	[1.4]	[1.4]	[0.7]	[1.4]				
IV (7–12)	J	–	–	–	3.08	4.51	5.15	4.38	D				16
		–	–	[2.3]	[2.8]	[2.8]	[2.1]	[0.7]					
	K	–	–	–	3.34	5.11	5.00	D			17		14
		–	[1.0]	–	[3.0]	[2.6]	–					7	
	L	–	–	1.70	2.70	2.18	–	3.30	3.18	1.70			S
		–	[1.4]	[2.1]	[2.1]	[2.3]	[1.7]	[0.7]	[0.7]	–			

– = Not detected. S = Survived. D = Dead.